Detection and Quantitation of Calcific Atherosclerosis by Ultrafast Computed Tomography in Children and Young Adults With Homozygous Familial Hypercholesterolemia

Jeffrey M. Hoeg, Irwin M. Feuerstein, Eben E. Tucker

Abstract Ultrafast computed tomography (CT) is a new method for detecting calcific lesions in the coronary arteries. The ability of CT to detect and quantify coronary artery atherosclerosis in children and young adults at risk for malignant atherogenesis was evaluated. A total of 11 consecutive familial hypercholesterolemic (FH) homozygotes (3 to 37 years old) participated. Untreated total cholesterol concentrations were 488 to 1277 mg/dL (12.7 to 33.2 mmol/L). Angiography detected significant lesions in 7 of 11 patients. CT detected calcific atherosclerosis in all 9 of the patients older than 12 years of age, including all those with angina. CT was more sensitive in detecting aortic root and coronary ostial lesions; where atherosclerosis first appears in homozygous FH. The volume of calcification (in cubic millimeters) correlated with the severity and duration of the hypercholesterolemia ($r=.62$, $P<.05$) as well as with the presence of angina ($P<.05$). All patients with angina (7 of 7) had >150 mm^3 of calcified volume, whereas only 1 of 4 asymptomatic patients had a volume score >150 mm^3. We conclude that (1) coronary and aortic calcium phosphate deposits are common in young FH homozygotes; (2) these deposits are associated with the presence of angiographic stenoses, as has been seen in adults with coronary atherosclerosis; and (3) aortic calcific deposits are more common than calcific coronary lesions. (*Arterioscler Thromb.* 1994;14:1066-1074.)

Key Words • lipoproteins • familial hypercholesterolemia • atherosclerosis • computed tomography • diagnostic imaging

The inborn error in cholesterol metabolism that has provided the greatest insight into the role of low-density lipoprotein (LDL) cholesterol in human atherosclerosis is that of familial hypercholesterolemia (FH). More than 150 specific mutations in the LDL receptor gene have been identified that lead to deranged clearance of atherogenic, cholesteryl ester–rich LDL particles from the circulation.[1] Patients heterozygous for this disease, in whom only one allele is affected, represent approximately 1 in 500 individuals in the population.[2,3] However, the homozygous form of the disease is extremely rare. Fewer than 1 case is estimated to occur for each million births in the United States. Despite the rarity of this condition, investigation of homozygous FH has led to an array of insights into the pathophysiology of atherosclerosis, the role of LDL in cholesterol transport, the cellular process of receptor-mediated endocytosis, and treatment strategies to prevent cardiovascular disease.[4]

We have turned once again to patients homozygous for FH to address an emerging issue in the prevention and treatment of cardiovascular disease. Physicians are now encouraged to screen for patients likely to benefit from diet and drug therapy to prevent the development of atherosclerotic cardiovascular disease,[5] most notably coronary artery disease (CAD). A variety of risk stratification recommendations have been made to attempt to effectively identify those patients most likely to benefit from treatment and to avoid needless intervention in asymptomatic individuals.[5-7] The detection of coronary artery atherosclerosis by screening for calcific density with fluoroscopy was first suggested to be useful in 1927.[8] Subsequent studies during the past 65 years have delineated the presence of coronary artery calcification of patients postmortem[9-11] and radiographically[12-19] and have correlated the severity of the coronary atherosclerosis and clinical events with the degree of calcification.[9,13,14,17,19-22] Since medial calcific sclerosis does not involve the coronary arteries, calcifications in these vessels are diagnostic and pathognomonic for atherosclerosis. Using an ultrafast computed tomography (CT) scanner with a 100-millisecond acquisition time, 3-mm slice thickness, and 1-mm in-plane spatial resolution, it has been possible to quickly detect and quantitate coronary artery calcific deposits.[23-26] Agatston and associates[27] demonstrated that quantitative calcific plaque scoring of lesions has a specificity of 70% to 90%, a sensitivity of 71% to 74%, and a negative predictive value of 94% to 100% for symptomatic CAD in patients 30 to 69 years of age. Therefore, CT holds promise for assessing the atherosclerotic process in asymptomatic individuals.

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TABLE 1. Characteristics of Children and Young Adults With Homozygous Familial Hypercholesterolemia

Patient No.	Age, y	Sex	Age at Diagnosis, y	Untreated Cholesterol Concentration, md/dL			TC/HDL	Lp(a), mg/dL	Cholesterol-Years, mg-y/dL
				Total	LDL	HDL			
1	3	M	1	724	672	28	25	9	2 172
2	7	F	<1	888	841	21	42	0	6 216
3	12	M	4	578	535	32	18	132	6 936
4	13	F	1	906	795	32	28	122	11 778
5	15	M	4	969	841	43	16	50	12 606
6	18	M	2	1277	1153	17	75	5	16 584
7	27	F	3	612	572	28	21	66	9 456
8	29	F	7	488	447	29	15	41	12 416
9	34	M	21	711	536	56	10	3	18 162
10	35	F	9	740	534	33	22	29	23 170
11	37	F	12	713	650	33	22	108	19 849
Mean±SD	21±12		6±6	782±219	671±198	32±10	27±18	52±49	12 668±6 349

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; and Lp(a), lipoprotein(a).

The children and young adults evaluated and treated for homozygous FH at the Clinical Center of the National Institutes of Health provide a population in which to compare methods to screen for atherosclerosis. We have undertaken a systematic analysis of the ability of ultrafast CT to detect and quantify atherosclerosis in children and young adults homozygous for FH.

Methods

Patients

Consecutive patients homozygous for FH (n=11; 5 males, 6 females) participated in this study at the Clinical Center of the National Institutes of Health. These patients were diagnosed as having homozygous FH based on their plasma lipoprotein concentrations (Table 1), family history, and the presence of tuberous and tendinous xanthomata. The patients ranged in age from 3 to 37 years, with an average age of 21.8±12 years. The average age at the time of diagnosis was 6±6 years. Their fasting total and LDL cholesterol concentrations before treatment were profoundly increased. Patients >5 years of age underwent percutaneous coronary arteriography within 12 months of the CT study. Left heart catheterization and coronary arteriography were performed using standard techniques.[28] Significant lesions were defined as those with >50% luminal diameter (or 75% luminal area) stenosis. The study was approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute.

Lipoprotein Assays

The fasting total, LDL, and high-density lipoprotein (HDL) cholesterol concentrations were determined by enzymatic assays as outlined previously,[29] and the concentration of lipoprotein(a) [Lp(a)] was determined by a sandwich enzyme-linked immunosorbent assay as previously described.[30]

Because of the profound elevations in the concentrations of atherogenic lipoprotein particles, these patients have received a number of therapies, including a variety of hypolipidemic medications, ileal bypass, liver transplantation, LDL apheresis, and plasma exchange. The "cholesterol-years" score is an estimate of the lifelong total vascular exposure to the profound hypercholesterolemia in these patients. This cholesterol-years score was calculated as follows. The total cholesterol concentration (in milligrams per deciliter) of each patient at the time of original diagnosis was multiplied by the age of the patient at diagnosis. The total cholesterol concentration present in the patient after therapy was then multiplied by the number of years of treatment. The pretreatment and posttreatment cholesterol-years (mg-y/dL) were then added together for the total cholesterol-years score.

Ultrafast Scans

Ultrafast CT of the heart and thoracic aorta was done in all 11 patients. Scans were performed on the Imatron C-100XL CT scanner (Imatron Co). No intravenous contrast material was used. Scans were acquired using the 100-millisecond, high-resolution mode with table incrementation. Scan parameters were fixed at 130 kV and approximately 625 mA. A 26-cm reconstruction circle and 512×512 reconstruction matrix were used. Scans were cardiac gated, triggered at 80% of the RR interval for every other heartbeat. Each scan sequence was performed during a single breath hold of approximately 25 to 30 seconds. The upper thoracic aorta was scanned from above the arch down to the right pulmonary artery using 6-mm-thick contiguous sections. The coronary arteries, heart, and descending aorta were then scanned using 3-mm-thick contiguous sections starting at the right pulmonary artery and scanning caudally for 40 slices. Additional sections were added as needed to scan completely through the heart and descending thoracic aorta.

Calcification scoring of the coronary arteries and aorta was done at the Imatron console using standard ultrafast CT quantification schemes, with minor modifications tailored to address the calcific lesions in the aortic root. A calcification was defined as an area with at least four contiguous pixels (1 mm^2) in any given slice having density values ≥130 Hounsfield units (HU). Detection of the appropriate pixels was facilitated by the identify function, which brightly highlights all pixels within the desired density range. Each calcified area was evaluated by two different techniques. First, a commonly used index of the relative severity of calcification, termed the calcification score, was calculated as the product of the area of calcified tissue (HU ≥130) multiplied by a weighting density factor (1+, 130 to 199 HU; 2+, 200 to 299 HU; 3+, 300 to 399

HU; and 4+, ≥400 HU). A second measure, the calcified volume score, which represents the total volume of calcified tissue in cubic millimeters, is computed by summing the volume of calcified tissue in each individual lesion. Each volume was calculated by multiplying the calcified area of a lesion by slice thickness (in millimeters).

The anatomy was divided into the coronary arteries and the aorta. The scores were collated for the individual left main, left anterior descending, left circumflex, right, and posterior descending coronary arteries, and the sum of the scores from these arteries is reported as the CAD score. The aorta was divided into the aortic root, the rest of the ascending aorta, and the descending aorta. The aortic root was defined as the section of ascending aorta within 20 mm (six sections) of either coronary ostium. The aortic root was further subdivided into left ostial, right ostial, and paraostial areas, and the aortic root score is the total of these three areas. Lesions were defined as ostial if the calcified plaque was in direct contact with the coronary ostium. Paraostial lesions were those calcified plaques within 20 mm of the coronary ostia that were not ostial. The aortic root slices were always made with 3-mm-thick sections. It was not unusual for an ostial plaque to seamlessly blend with a proximal coronary artery plaque. Following accepted practice, the ostial and coronary plaques were disarticulated and scored separately. For those sections through ascending aorta using 6-mm slices, the scores were doubled to compensate for the lesser number of slices. The descending aorta score was derived from a combination of 3- and 6-mm sections. The "total" scores represent the sum of the scores of all the regions in the coronary arteries (the CAD score) and aorta.

Correlations of the atherosclerosis risk factors with the different lesion scores were performed by two-tailed linear regression analyses; significant correlations are defined as $P<.05$. Comparison of the calcified volume scores in patients with and without symptomatic angina was made using the two-tailed Wilcoxon rank sum test.

Comparisons between CT and aortocoronary arteriography were also made. For CAD, coronary arteriography was considered the reference standard for occlusive disease, and significant lesions were defined as those with >50% luminal diameter (or >75% luminal area) stenosis. Arteriograms were designated as positive or negative for CAD. Similarly, a CT was designated as positive or negative for coronary atherosclerosis based on the calcification score. A score <5 was never significant. For ages <30 years, any score >5 was positive. For ages >30 years, any score >20 was positive. For the aortic root, including the areas around the coronary ostia, the CT scan was considered the standard of reference. There are no established criteria for positivity, but as it turned out, all of the studies were clearly either positive or negative, with no marginal scores. The aortograms were not quantified and were judged as simply positive or negative.

A control group was studied retrospectively to determine age-related population patterns of aortic and coronary calcifications. Since an optimal group of normal young patients who had undergone extensive cardiac scanning did not exist, patients were taken from a CT logbook covering a several-month period of routine work on the Imatron scanner. To be included, patients must have undergone ultrafast CT of the chest without injection of intravenous contrast material. All scans were performed with 6-mm-thick sections, with either 8- or 10-mm scan spacing. Most scans used a 300-millisecond duration. Cardiac gating was not used. Exclusion criteria included primary diagnoses in which mediastinal irradiation is common. The control patients were divided into two subsets. First, to approximate the ages of our FH patients, a subset of 29 patients aged 0 to 40 years was culled. Unless specified otherwise, references to control subjects in the rest of the study refer to this control group. Second, to check the ability of the altered scan parameters to detect coronary calcification, scans from 24 patients >40 years old were obtained. Consecutive patients were obtained except in the group aged 20 to 29 years, in which random, nonconsecutive patients were sought to compensate for the low number of patients obtained by chance. For each, a visual extent of lesions score was calculated for both the aorta and the coronary arteries.

For illustrative purposes, three-dimensional images were constructed and compared with angiography for selected cases. The axial Imatron scans were transferred to a Voxelscope II three-dimensional imaging work station (Picker International). The coronary arteries and ascending aorta were separated (disarticulated) from the surrounding, overlying tissues. Rendering windows were chosen to eliminate surrounding fat. The internal coronary artery calcifications were imaged through the arterial walls using the transparency function, and the final image was photographed.

Results

Laboratory Findings

The clinical characteristics of the patients participating in this study are detailed in Table 1. The concentrations of plasma lipoproteins were strikingly altered in these patients. The average total and LDL cholesterol concentrations were more than threefold higher than the "desirable" concentrations outlined by the Adult Treatment Panel of the National Cholesterol Education Program.[5] In addition, HDL cholesterol was depressed. Therefore, the average ratio of total cholesterol to HDL cholesterol of 27 was more than fivefold higher than for average cardiovascular disease risk. The concentration of Lp(a), a lipoprotein particle proposed to be prothrombogenic,[31-33] ranged from 0 to 132 mg/dL. Two thirds of the population has concentrations of <20 mg/dL,[34] whereas 6 of 11 of these patients exceeded this concentration. The cholesterol-years scores, which integrate the lifetime cholesterol exposure over the varying levels before and after therapy, spanned a wide range, from 2172 to 23 170 mg-y/dL (56.5 to 602.4 mmol-y/L), with a mean score of 12 668 (329.4 mmol-y/L). Since most of the total cholesterol concentrations of these patients were carried in LDL, this score largely reflects the exposure of the vasculature to this atherogenic lipoprotein particle.

Coronary Artery Assessment

All patients >5 years of age underwent cardiovascular evaluation by both cardiac catheterization and CT. One 3-year-old boy underwent CT only. The data are divided into coronary artery analysis in this section and aortic analysis in the next section. Coronary artery lesions were detected by both angiography and CT (Table 2). Of the patients catheterized, 7 of 10 were positive for significant obstructive lesions that reduced the coronary artery lumen by >50% cross-sectional diameter (or 75% luminal area). CT was positive for significant coronary calcification in 5 of 7 patients with angiographic stenosis. The 2 of 7 missed by CT were both <15 years old, and 1 was asymptomatic. One of the 3 patients with arteriograms negative for significant CAD had 71 U of calcium on CT. Since CT is more sensitive for coronary artery calcium than cardiac fluoroscopy, this is considered significant, representing preocclusive atherosclerosis.

TABLE 2. Coronary Artery Disease in Homozygous Familial Hypercholesterolemia Patients Assessed by Computed Tomography and Cardiac Catheterization

Patient No.	Age, y	CT Calcification Score				CT Calcified Volume, mm³				Cath Lesions	Angina
		CAD	Ostia	Aortic Root	Total	CAD	Ostia	Aortic Root	Total		
1	3	0	0	0	0	0	0	0	0	ND	No
2	7	0	0	0	0	0	0	0	0	+	No
3	12	0	0	0	0	0	0	0	0	0	No
4	13	1	73	166	254	3	73	159	251	0	Yes
5	15	0	1022	2091	2104	0	787	1697	1722	+	Yes
6	18	11	138	744	2795	17	124	607	1818	+	Yes
7	27	71	203	248	449	57	193	403	578	0	No
8	29	274	306	383	658	973	268	344	1317	+	Yes
9	34	96	0	49	147	115	0	69	186	+	Yes
10	35	247	806	1109	1356	256	684	941	1197	+	Yes
11	37	12	594	1659	1737	19	462	1270	1399	+	Yes
Mean±SD		65±102	286±361	586±732	863±985	131±290	234±283	499±576	770±729		

CT indicates computed tomography; CAD, coronary artery disease; Cath, catheterization; and ND, catheterization not done. Presence (+) or absence (0) of lesions with >50% luminal diameter occlusion was determined by coronary arteriography.

Table 2 includes CT measures of coronary artery calcification scores. For the FH patient population the score was 65±102, and the volume of calcification was 131±290 mm³. Means for control subjects were both 0 ($P<.001$, unpaired t test). The severity of the calcific lesions defined by both the calcification score and the calcified volume score was significantly higher ($P<.05$, Wilcoxon rank sum test) in those patients with angiographically evident CAD (91±120 and 197±355 mm³, respectively) than in those without lesions (18±35 and 20±32 mm³, respectively). Four of 11 (36%) of the total group and 4 of 7 (57%) of the patients with angina had elevated coronary artery calcification scores. The 3 of 7 patients with angina and low CAD scores had heavy aortic root and ostial calcification, however (see below).

Although a systematic, lesion-by-lesion comparison between arteriography and CT was not performed for all coronary arterial lesions, for specific cases direct comparisons were made. For example, the three-dimensional images of the coronary artery anatomy of patient 8 by CT and by angiography have been directly compared (Fig 1). The coronary artery lesions resulting in >50% luminal diameter stenosis defined by angiography and those of CT correlate well, although the degree of stenosis can be determined only on the arteriograms. The extent of nonocclusive atherosclerosis and marked right and left ostial plaque were clearly more evident on the CT image than on the angiographic image.

Aortic Root Findings

The analysis of calcific arterial lesions by CT was particularly effective for detecting and quantitating the severity of lesions in the coronary ostia and in the aorta (Fig 1A, Table 2). Quantitation of these lesions by both the calcification score and the extent of lesion score indicated that the burden of overall vascular disease was largely in the ascending aorta, particularly in the aortic root. The aortic root calcification score in FH patients was 586±732, and the calcified volume of lesions was 499±576 mm³. This is compared with control CT scans from 29 age-matched (<40 years old), non-FH patients, 28 of whom had total and calcified volume scores of 0 ($P<.0001$, unpaired t test). Only one 34-year-old woman was found to have any calcific lesions using these methods, and she had an aortic lesion score of 2.

The distribution of calcifications appears to be predictable and age related in these patients. The pattern is centrifugal, in that with increasing age the burden of calcification becomes more prominent distally, moving from the aorta and coronary ostia into the coronary arteries (Fig 2). The greatest degree of calcification defined by both the calcification score and the calcified volume score was observed in the ascending aorta, particularly in the ostial and paraostial regions, and the total calcified volume is largely a reflection of aortic lesions (Table 2). Seven of the 8 patients (88%) with detectable calcium demonstrated more calcification in the aorta than the coronary arteries. The other patient was unusual in that his cholesterol levels were extremely well controlled, and in that regard he was more like the general population than a patient with FH (patient 9, Table 1). Similarly, in 7 of 8 patients with calcified lesions, at least half the calcification was in the aggregate ostial and paraostial zones. The remaining patient, with the highest aortic and overall scores of all (patient 6), had extensive ascending aortic calcium in addition to copious ostial and paraostial disease. The effect of age is also shown by Table 2. The youngest 6 patients had virtually no coronary calcification, their disease clearly showing preference for the aortic root and coronary ostia. Only after age 20 do patients begin to show significant calcification and extent of lesion scores in the coronary arteries themselves.

Calcified lesions were seen by CT only in patients aged ≥13 years. In those younger, CT was negative in the only patient with known CAD. The number of patients aged

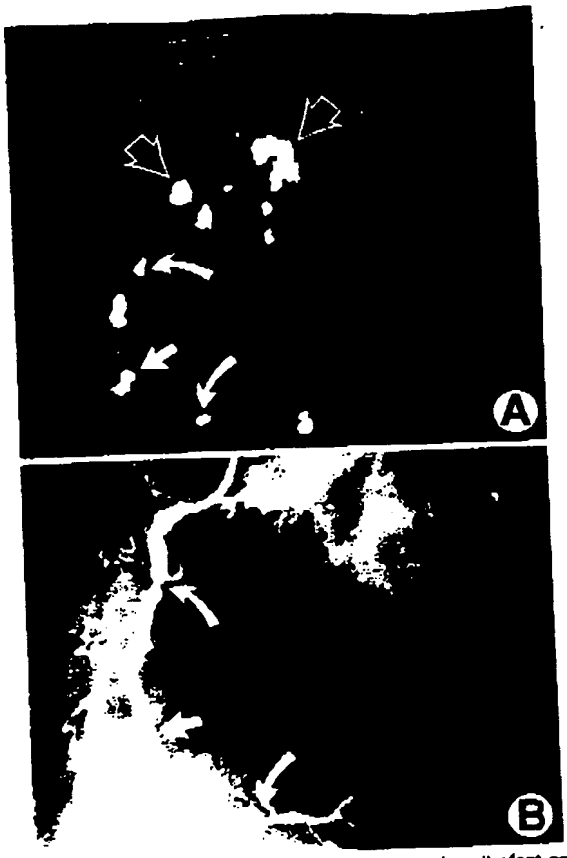

FIG 1. Identification of calcific atherosclerosis by ultrafast computed tomography (CT) (A) and by cardiac catheterization (B). Lesions were observed using both techniques. The coronary artery lesions resulting in >50% luminal diameter stenosis of the right coronary artery as defined by angiography in the left anterior oblique position are highlighted by the solid, curved white arrows (B). The three-dimensional image of the heart of this same patient in the same orientation was able to place calcification of these same stenotic lesions, again highlighted by the solid curved white arrows (A). A lesion that partially encroached on the lumen as seen by angiography was also detected by CT (straight white arrow). However, the extent of nonocclusive atherosclerosis was more fully evident in the CT image than in the angiographic image, since ultrafast CT detected calcific lesions in both the right coronary artery and the coronary ostia (A; open arrows), which are not apparent by coronary arteriography. In the angiogram, for example, there is a hint of luminal irregularity that does not reach critical stenosis (B; short, solid arrow) but is detected by CT.

<13 years was too small to analyze, but it remains to be determined whether CT can successfully detect atherosclerosis in this younger age subpopulation.

Relation of CT Findings to Clinical Parameters

The correlation coefficients of the CT findings with atherosclerotic risk factors are illustrated in Table 3. The best correlation with CAD scores was with the age of the patient ($r=.62$, $P<.05$). Even in these profoundly hypercholesterolemic patients, the total and LDL cholesterol concentrations at the time of initial diagnosis were not highly correlated with CAD scores. Calcifications became apparent in the coronary arteries by age

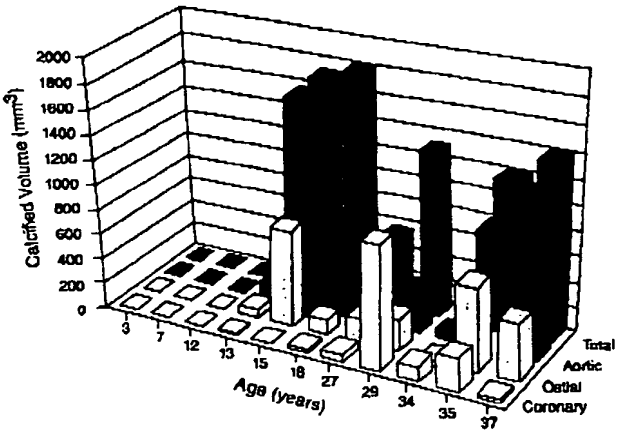

FIG 2. Graph shows extent of calcific lesions in patients ranked by age. The calcified lesion volume in the coronary arteries (coronary), the coronary ostia (ostial), the ascending aortic root (aortic), and the total extent of lesions (total) are illustrated for each patient identified by age. Lesions were detected in the aorta (as reflected in the total score) in all but the youngest patients. Older patients expressed calcific lesions in the coronary ostia as well as in the coronary arteries.

13 and increased through the 20s and early 30s (Fig 3). This apparent lack of correlation was affected by the low calcification score in patient 11, the oldest patient in this study. This patient may not be entirely representative, since she had received partial ileal bypass surgery as a child and had experienced a 23% reduction in her total cholesterol concentration from this procedure.

The degree of calcific atherosclerosis in the ostia and aortic root was particularly striking in these homozygous FH patients. Since normolipidemic children and young adults have aortic calcification scores of 0, these data indicate that profound hypercholesterolemia leads to more marked lesion formation in the aortic root than in the coronary arteries. The best correlations between the severity of calcific atherosclerosis in the ostia (Fig 4) and with the total calcified volume (Fig 5) was the cholesterol-year score. This was more significant than the correlation of the other potential modifiers of the atherosclerotic process, including HDL and Lp(a). The HDL cholesterol concentration in these patients was low, with a mean concentration of 32±10 mg/dL (0.83±0.26 mmol/L). But even with the range of HDL concentrations from 17 to 56 mg/dL (0.44 to 1.46 mmol/L), the HDL cholesterol concentration and th ratio of total cholesterol to HDL cholesterol were not well correlated with the development of lesions. Lp(a), a lipoprotein particle that may promote intravascular clot formation, ranged in concentration from 0 to 132 mg/dL in this patient population. Despite this wide range, there did not appear to be any correlation between this particle concentration and calcific lesion formation.

The presence of aortic lesions by CT correlates well with the presence of symptomatic cardiovascular disease. The aortic calcification score for the patients with symptoms (1201±1040) was much higher than in asymptomatic patients (129±154; $P<.05$). In contrast, the degree of coronary calcification does not correlate as

TABLE 3. Correlations f C mputed Tomographic Findings With Atherosclerotic Cardiovascular Diseas Risk Factors

	CT Calcification Scores				CT Calcified Volume			
	CAD	Ostia	Aortic Root	Total	CAD	Ostia	Aortic Root	Total
Age	.62*	.41	.36	.29	.39	.51	.40	.45
TC	−.47	.09	.29	.63*	−.49	.02	.26	.38
LDL	−.54	−.23	.01	.46	−.46	−.26	−.02	.20
HDL	.12	.23	.18	−.16	−.01	.17	.17	−.11
TC/HDL	−.32	−.24	−.05	.48	−.27	−.22	−.06	.28
Lp(a)	−.23	.07	.11	−.12	−.14	.08	.10	.09
Cholesterol-years	.45	.54	.55	.59	.17	.62*	.56	.62*

Regression analysis *r* values are given for total (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol concentrations, TC/HDL ratio, and lipoprotein(a) [Lp(a)] levels vs coronary artery (CAD), ostial, aortic, and total calcific atherosclerosis defined by computed tomography (CT).

*Significant correlation ($P<.05$) by linear regression analysis.

well with the presence of symptoms and may not reflect small but dangerous nonstenosing lesions. Cholesterol-years also correlated well with calcified volume and was significantly associated with the presence or absence of angina ($P<.05$) (Fig 5). All of the patients with extent of lesion scores >150 mm^3 have developed angina. In contrast, 4 of 5 of the patients with scores <150 mm^3 have not developed angina.

Discussion

The most profoundly elevated concentrations of LDL are present in individuals totally lacking functional LDL receptor genes.[4] These patients homozygous for FH have been noted to have angina pectoris, aortic stenosis, supravalvular aortic stenosis, aortic insufficiency, and sudden cardiac death as children and young adults.[35-39] The most aggressive forms of therapy, including plasma exchange, LDL apheresis, and liver transplantation, have been successfully applied to patients experiencing the most aggressive form of this disease.[40-43] Therefore, early detection of aggressive atherosclerosis in these patients would permit the application of experimental therapy before the signs and symptoms of atherosclerosis develop. The use of a noninvasive technique would permit the detection and sequential evaluation of these patients prone to early cardiovascular disability and death.

One means of screening for accelerated atherosclerosis is to detect lesions that have become calcified. Although patients could be categorized as being either positive or negative for coronary calcification by fluoroscopy,[12,19,21] digital subtraction fluoroscopy,[18] fluoroscopy plus cineangiography,[13,22] and conventional CT,[44] the ability to accurately detect and quantitate lesions became available only with the use of ultrafast CT in 1989.[24] Subsequently, a number of reports have demonstrated that ultrafast CT, which acquires images in 100 milliseconds gated to the electrocardiogram, is a sensitive technique for detecting coronary artery calcification as well as for quantitating the degree of lesion calcification.[24,26,27,45] The major focus of these efforts was to compare CT-defined lesions with those seen at coronary angiography, with the implicit assumption that a noninvasive coronary angiogram could be developed. Agatston et al[27] reported that for 110 healthy individu-

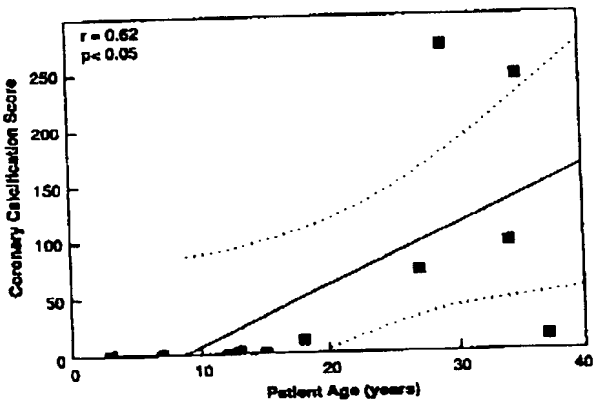

FIG 3. Plot shows coronary artery calcification score vs age. The score for each patient as a function of years is shown. The dotted lines represent the 95% confidence interval; the correlation was statistically significant ($P<.05$).

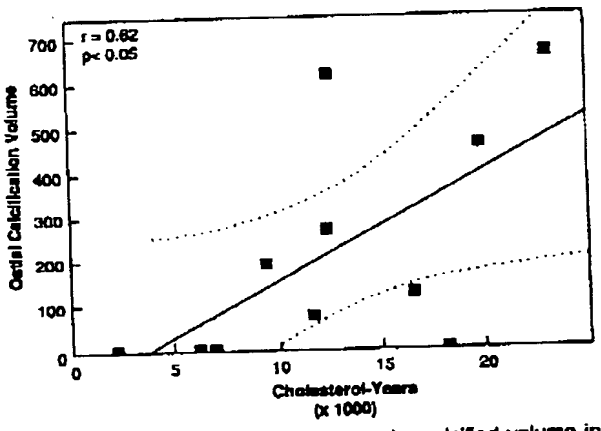

FIG 4. Plot shows correlation between the calcified volume in the coronary ostia and cholesterol-years. The values represent the cholesterol-years of exposure and the total extent of calcific lesions for each patient. The dotted lines represent the 95% confidence intervals; the correlation was statistically significant ($P<.05$). To convert cholesterol-years from mg-y/dL to mmol-y/L, divide the score by 38.46.

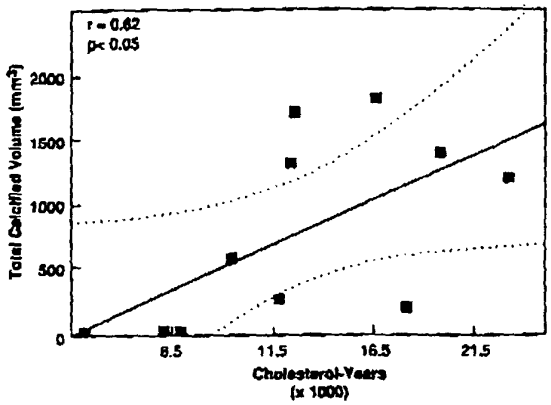

Fig 5. Plot shows comparison of the calcified volume of calcific lesions with cholesterol-years of exposure. The dotted lines represent the 95% confidence intervals; the correlation was statistically significant ($P<.05$). To convert cholesterol-years from mg-y/dL to mmol-y/L, divide the score by 38.46.

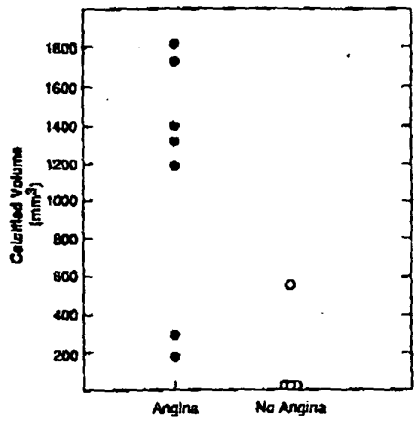

Fig 6. Plot shows comparison of the total extent of calcific lesions present in homozygous familial hypercholesterolemic patients who have (●) and have not (○) developed angina. The lesion scores for the patients without angina were significantly lower than in symptomatic patients as assessed by a two-tailed Wilcoxon rank sum test ($P<.05$).

als 30 to 39 years of age, the coronary artery calcification score was 5±2. The 3 patients in the same age group who manifested CAD had substantially higher scores (132±91). Our findings in young control patients closely parallel these findings. The coronary calcification score in our FH patients using the same grading system was 65±102 (Table 2), with the symptomatic patients having substantially higher scores than the asymptomatic patients. Therefore, coronary calcific lesion scoring is indeed a discriminator for the presence of angina. An additional hypothesis is that, at some point, calcification should be predictive for development of angina in those FH patients who have not yet developed symptoms. On the other hand, the correlation between density of calcification and degree of occlusion for a specific lesion is weaker, and CT cannot replace angiography to evaluate the degree of luminal obstruction.[46,47] Furthermore, the calcific lesions may not reflect lesions prone to rupture. Therefore, CT should be considered complementary in the detection of atherosclerosis in patients.

Some limitations inherent in the present study limit the generalizability of these findings. First, the striking aortic atherosclerosis that these patients manifest may not be representative of more common forms of atherosclerosis. However, the limited number of calcific lesions detected in the 28 control patients <40 years of age suggests that this is not commonly detected. Only additional investigation with this technique will reveal the utility of aortic root screening in more common clinical contexts. Another limitation is that only calcific lesions are detected with this technique. Atherosclerosis begins with lipid deposition in children and young adults in the general population,[48] and only later are calcific changes seen. Therefore, this technique only detects a subpopulation of advanced, mature lesions. Our youngest patient with angiographically defined obstructive CAD had no calcifications at CT, presumably due to an immature, noncalcified, "soft" plaque. The lower limit of the evaluable age range for CT efficacy has not yet been determined. Further investigation is required to prospectively evaluate the prognostic and clinical utility that detection of advanced lesions signifies in the prevention of cardiovascular disease sequelae.

Our findings in young patients homozygous for FH have a number of both theoretical and practical ramifications. We have observed that the earliest indication of accelerated atherosclerosis is in the aortic root and at the coronary ostia, evidenced by localized predominance in the younger subset of patients. This focuses enhanced attention on the aorta, which contrasts with most previous work that has concentrated on the coronary artery lesions. Although aortic calcification has long been known to occur,[5] these are the first data (Table 2, Fig 2) to suggest that screening patients for a diathesis toward malignant atherosclerosis is best directed toward identifying and quantitating calcific aortic atherosclerotic plaque. This is clinically relevant because the formation of these calcific lesions appears to presage the development of symptomatic coronary artery disease in FH patients (Fig 6). These findings then shift the emphasis and goals of noninvasive imaging strategy in FH patients. Previously, symptomatic patients were evaluated using magnetic resonance imaging[49] and ultrafast CT as surrogates for arteriography. Instead, these findings suggest that CT is a complementary technique to detect the atherosclerotic process during its "silent," presymptomatic stage.

A second practical issue relates to the therapeutic decisions that must be made in these homozygous FH patients. Previous novel treatment attempts for this disease were restricted to patients with severe end-stage cardiovascular disease. Liver transplantation, for example, was attempted only in homozygous FH patients who were close to death.[40,42] Therefore, the use of a CT-derived score could facilitate the identification of patients likely to develop the sequelae of hypercholesterolemia before myocardial infarction. In addition, the CT lesion score will facilitate the treatment of FH patients with more conventional methods. Since plasma exchange and LDL apheresis are the current treatments

of choice for this disease,[43] the timing related to instituting these costly and time-consuming procedures may be facilitated using the CT results. Ultrafast CT provides an independent means by which the calcium in nonocclusive lesions could be quantitated, providing additional information about the overall burden of atherosclerosis not available by fluoroscopy or angiography. Once the calcified volume exceeds 150 mm^3 (Fig 6), the probability of developing angina markedly increases, and efforts at aggressive treatment would be of benefit. Assessment of other treatment modalities in these patients, such as liver transplantation,[40,42] portacaval shunting,[41] and gene therapy,[50,51] could also benefit from the use of CT. The calcification score could not only help to select patients for treatment protocols but might also be a means of assessing the impact of therapy on the rate of progression (changing the slope of the regression lines in Figs 4 and 5) or the regression of atherosclerotic lesions.

One of the most interesting theoretical developments that emerged from this study is the utility of cholesterol-year risk. The most significant predictor of the severity of the coronary artery calcification score was age; the total plasma cholesterol concentration did not significantly correlate with calcific lesion formation (Table 3). However, by combining these two variables into a single formula, one integrates the lifelong endothelial exposure to atherogenic lipoproteins, which not only improves the statistical correlation (Figs 4 and 5) but also has biologic plausibility. Using this concept, calcific atherosclerosis does not appear below an apparent threshold of <7000 cholesterol-years (182.0 mmol-y/L). Of course, atheromatous plaque formation most likely occurs long before sufficient calcium has been deposited to be detectable by CT. However, it may become useful to extend the concept of cholesterol-year as well as the technique of ultrafast CT beyond homozygous FH.

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